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## METHOD OF INTRODUCING DEUTERIUM INTO ORGANIC COMPOUNDS

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### 1. Title of Invention

Method of Introducing Deuterium into Organic Compounds

### Detailed Explanation of Invention

Until now, several methods of synthesizing organic compounds including heavy hydrogen have been known, but a general method of manufacturing various organic compounds that include a high content of heavy hydrogen is so far unknown. In the methods of Prior Art, in many low molecular weight compounds, it was possible to replace hydrogen completely with deuterium, but in high molecular compounds it was impossible to accomplish a complete replacement directly. This invention concerns a general method that enables the replacement of light hydrogen with a heavy hydrogen isotope in numerous organic compounds including high molecular weight compounds. This new method can be used to manufacture heavy hydrogen containing compounds on a small scale experimentally and, moreover, it can be used for manufacturing on an industrial scale.

By complying with this invention, immediate substitution of light hydrogen with deuterium is possible using appropriate sources of heavy hydrogen (e.g., deuterium).

In the initial attempts at substituting light hydrogen with deuterium, organic compounds were treated with heavy water in the presence of an alkali and platinum catalyst. This method can achieve the replacement of mobile hydrogen atoms but it cannot achieve a complete substitution of all hydrogen atoms in a high molecular compound.

The authors of this invention learned that to carry out a complete substitution, it is necessary to further add a reaction catalyst (referred to here as a promoter).

The method of this invention is characterized in that, in the course of a direct substitution reaction that occurs between an organic compound that contains light hydrogen and a source of heavy hydrogen, such as deuterium oxide, in the presence of an alkaline metal deutoeroxide and a reduced Adams catalyst ( $\text{PtO}_2 \cdot \text{H}_2\text{O}$ ), deuterium peroxide is added as the reaction promoter.

The method of this invention can be used to manufacture, for example, a completely deuterated aliphatic acid, dicarboxylic acid, ketone, alcohol, and a variety of hydrocarbons; therefore, it has broad applicability. This method can be used to produce deuterium-containing compounds with a high degree of isotope purity (99% or more), and this degree of isotope purity is limited only by the degree of isotope purity of the deuterium source.

In the presence of deuterium peroxide and a metal catalyst (Adams platinum catalyst, etc.) the starting compound (an organic compound that contains light hydrogen) is heated in a solution of alkaline deuterioxide in deuterium oxide. This heating is carried out in a tightly sealed container and accompanied by shaking and mixing. A deuterated compound is separated from the resulting reaction mix by conventional methods and can be regenerated into an active form. The alkaline base metal also can be recovered as needed.

Regarding the amount that can be substituted in a one-time operation, a few factors are important: temperature, the relative amount of catalyst, heating time, etc. The properties of the metal catalyst and the structure of the organic compound are also of importance.

Research concerning the kind of metal catalyst resulted in the finding that when the platinum oxide catalyst well known under the name Adams catalyst reduces ( $\text{PtO}_2 \cdot \text{H}_2\text{O}$ ) suspended in  $\text{D}_2\text{O}$  by means of deuterium gas, the product is very active as a deuterium reduction type, and therefore it is clear that it can be used as the catalyst in this invention. The alkaline deuterioxide and deuterium peroxide can be produced by a reaction between a metal peroxide and deuterium oxide. Then it is advantageous to use granular sodium peroxide. In the reaction of sodium peroxide and heavy water, equivalent amounts each of sodium deuterioxide (alkaline catalyst) and deuterium peroxide (promoter) are formed, but of course the weight ratio between the base catalyst and the promoter can be changed.

In the event that a small amount of perdeuterated organic compound is produced, a reaction tube made of thick hard glass, such as Pyrex, can be used, but this tube must be used only once. In the event of large-scale production a heating pressure-vessel with inert interior is needed. In the event of the previously mentioned glass reaction tube, the tube inside a thermostat-equipped oven must be placed on an efficient shaking mixer; and for large-scale operation, an appropriate apparatus must be provided to ensure effective mixing.

Next we will explain the production of various perdeuterated compounds by the method of this invention. In implementing this method, attention must be paid to the fact that the isotopes must not be diluted. In the examples, parts are parts by weight.

#### Example 1. Production of perdeuterated octadecanoic acid

##### (A) Preparing the metal catalyst

24.5 parts Adams catalyst ( $\text{PtO}_2 \cdot \text{H}_2\text{O}$ ) and 100 parts heavy water (99.78%  $\text{D}_2\text{O}$  manufactured by Norsk Hydro) are placed in a reactor. After the air is expelled by vacuum, gaseous deuterium is introduced, and the container is shaken until all of the platinum oxide is reduced.

##### (B) Preparing alkaline catalyst and promoter

15.5 parts granular sodium oxide (analytical grade  $\text{Na}_2\text{O}_3$  produced by Merck Co.) was carefully added in small increments to 1000 parts heavy water while cooling. The solution thus obtained theoretically includes 16.4 parts sodium deuterioxide and 7.2 parts deuterium peroxide that are used as the alkaline catalyst and promoter, respectively.

#### Exchange Reaction

In the reactor into which was placed said platinum catalyst reduced by deuterium were added successively 57 parts n-octadecanoic acid (stearic acid,) a solution of alkaline catalyst and promoter and 400 parts of heavy water and, once the entirety was cooled with dry ice, the air was expelled with vacuum and the container was sealed tight.

This vessel was heated to 240°C, and this temperature was maintained for 28 hours with vigorous agitation. After it had been cooled, the vessel was opened, and the resulting non-uniform mixture was stirred until it became uniform. The water was removed by evaporation at room temperature (a mixture of H<sub>2</sub>O and D<sub>2</sub>O.)

Another 1500 parts heavy water was added to the dry powder residue in the reactor, air was removed and the vessel tightly sealed. The second exchange reaction was carried out under the same conditions as the first one. Water was removed by evaporation, and upon acidifying with diluted hydrochloric acid, the organic phase was extracted with ether. The crude product thus obtained underwent chromatography in a silicic acid column.

Thus, 57 parts perdeuterated octadecanoic acid were obtained (90% of the theoretical quantity.) From the results of a mass-spectrographic analysis of the methyl ester thereof it was clear that this acid had more than 98% isotope purity.

A summary of the above-mentioned synthesis method would be as follows.

Table 1

第 1 表

化 合 物	M	分子 割合	重 量 部
CH <sub>3</sub> --(CH <sub>2</sub> ) <sub>16</sub> -COOH	284.468	2	57
D <sub>2</sub> O	20.028	1500	3000
Pt <sub>2</sub> O·H <sub>2</sub> O*	245.246	1	24.5
Pt	195.09	1	(19.5)
Na <sub>2</sub> O <sub>2</sub> *	77.994	2	15.5
NaOD	41.011	4	(16.4)
D <sub>2</sub> O <sub>2</sub>	36.028	2	(7.2)
OD <sub>3</sub> --(CD <sub>2</sub> ) <sub>16</sub> -COOH	319.678	2	(63.8)57

Columns [left to right]

Compounds; M; molecular content; weight parts

In the above-mentioned Table 1 and the following table, M denotes molecular weight, molecular content denotes the ratio of molecular weight.

The entire reaction time is 56 hours. The raw materials used for the catalyst and the promoter are designated with an asterisk. In the weight parts column, the numbers that are not in parentheses are the numbers that were actually used. The numbers in parentheses are theoretical values.

### Example 2. Preparing perdeuterated camphor

Camphor includes 3 perdeuterated methyl groups, and it is difficult to substitute their hydrogen atoms. In order to show that the method of this invention is effective in cases where such substitution is difficult, we carried out hydrogen – deuterium substitution immediately in a single operation. In this case, the reaction product was extracted from the reaction mixture by anhydrous ether. Based on this method 62 parts deuterated products was received from 60.8 parts camphor. Based on the analytical results obtained by means of gas chromatography it was clear that the product did not contain any byproducts. According to mass spectrometry the isoprenoid compounds included molecules  $C_{10}D_{16}O$ , but it was clear that  $C_{10}H_4D_{12}O$  accounted for most of it. The complete substitution rate in this single operation was 78% (based on mass spectrography).

A summary of the above synthesis method would be as follows.

Table 2

第 2 表

化 合 物	M	分子 割合	重 量 部
$C_{10}H_{16}O$	152.228	4	60.8
$D_2O$	20.028	1000	2000
$PtO_2 \cdot H_2O^*$	245.246	1	24.5
$Pt$	195.09	1	(19.5)
$Na_2O_2^*$	77.994	2	15.5
$NaOD$	41.011	4	(16.4)
$D_2O_2$	36.028	2	(7.2)
$C_{10}D_{10}O + \text{ジューーテリウム}$ 含量の低い類似 物	168.324	4	(67.2) 62

Columns [left to right]

Compounds; M; molecular content; weight parts

[In the left-hand column]

$C_{10}D_{10}O + \text{analogue with low deuterium content}$

### Example 3

Preparing perdeuterated anthracene

The synthesis was carried out under the same conditions as the in the above examples. In the event of anthracene, hydrogen atoms are easy to substitute and a fully deuterated product is obtained within one operation. To separate the target compound from the mixture obtained from the exchange reaction, water was evaporated ( $H_2O_2$ ,  $HDO$ ,  $D_2O$ ) whereupon it was extracted with dry benzene. Then the light yellow extract was condensed by evaporating at room temperature and the target polycyclic hydrocarbon

was precipitated. Thus from 53.4 parts anthracene, 48 parts (85%) high isotope purity (>99% based on mass-spectrography) perdeuterated anthracene was obtained.

A summary of the above synthesis method would be as follows.

Table 3

第 3 表

化 合 物	M	分子割合	重 量 部
$C_{14}H_{10}$	178.220	3	53.4
$D_2O$	20.028	1000	2000
$PtO_2 \cdot H_2O^*$	245.246	1	24.5
Pt	195.09	1	(19.5)
$Na_2O_2^*$	77.994	2	15.5
NaOD	41.011	4	(16.4)
$D_2O_2$	36.028	2	(7.2)
$C_{14}D_{10}$	188.280	3	(56.4) 48

Columns [left to right]

Compounds; M; molecular content; weight parts

A summary of the actual configuration of the embodiment of this invention is as follows.

1. In a method wherein in the presence of alkaline metal perdeuteroxide and a reduced Adams catalyst ( $PtO_2 \cdot H_2O$ ) organic compounds that lend themselves to deuteration, having hydrogen atoms that include hydrogen atoms that can be substituted with deuterium are reacted with heavy water as the source of deuterium and said organic compounds are deuterated, - an improved deuteration method characterized in that it is implemented in the presence of deuterium peroxide as the deuteration reaction promoter.
2. The method under Item 1 wherein sodium peroxide ( $Na_2O_2$ ) is added to react with heavy water ( $D_2O$ ) to form an alkali (NaOD) and the promoter ( $D_2O_2$ ).
3. The method of items 1 – 2 wherein the reaction is carried out in a tightly sealed vessel under vigorous shaking and heating.
4. The method of any of the above-mentioned items wherein a metal catalyst is used that is prepared by reducing the Adams catalyst ( $PtO_2 \cdot H_2O$ ) suspended in heavy water with deuterium.

#### Claims

- 1 In a method wherein in the presence of alkaline metal perdeuteroxide and a reduced Adams catalyst ( $PtO_2 \cdot H_2O$ ) organic compounds that lend themselves to deuteration, having hydrogen atoms that include hydrogen atoms that can be substituted with deuterium are reacted with heavy water as the source of deuterium and said organic

compounds are deuterated, - an improved deuteration method characterized in that it is implemented in the presence of deuterium peroxide as the deuteration reaction promoter.

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